APPENDIX C

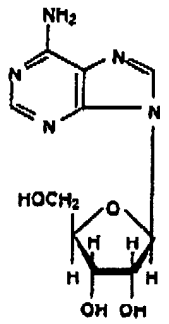
ADENOSCAN
(adenosine injection)

FOR INTRAVENOUS INFUSION ONLY

Revised. July 2005

DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-beta-D-ribofuranosyl-9-H-purine and has the following structural formula:



$C_{10}H_{13}N_5O_4$ 267.24

Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution.

Each Adenoscan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.

CLINICAL PHARMACOLOGY

Mechanism of Action

Adenosine is a potent vasodilator in most vascular beds, except in renal afferent arterioles and hepatic veins where it produces vasoconstriction. Adenosine is thought to exert its pharmacological effects through activation of purine receptors (cell-surface A_1 and A_2 adenosine receptors). Although the exact mechanism by which adenosine receptor activation relaxes vascular smooth muscle is not known, there is evidence to support both inhibition of the slow inward calcium current reducing calcium uptake, and activation of adenylate cyclase through A_2 receptors in smooth muscle cells. Adenosine may also lessen vascular tone by modulating sympathetic neurotransmission. The intracellular uptake of adenosine is mediated by a specific transmembrane nucleoside transport system. Once inside the cell, adenosine is rapidly

phosphorylated by adenosine kinase to adenosine monophosphate, or deaminated by adenosine deaminase to inosine. These intracellular metabolites of adenosine are not vasoactive.

Myocardial uptake of thallium-201 is directly proportional to coronary blood flow. Since Adenoscan significantly increases blood flow in normal coronary arteries with little or no increase in stenotic arteries, Adenoscan causes relatively less thallium-201 uptake in vascular territories supplied by stenotic coronary arteries i.e., a greater difference is seen after Adenoscan between areas served by normal and areas served by stenotic vessels than is seen prior to Adenoscan.

Hemodynamics

Adenosine produces a direct negative chronotropic, dromotropic and inotropic effect on the heart, presumably due to A_1-receptor agonism, and produces peripheral vasodilation, presumably due to A_2-receptor agonism. The net effect of Adenoscan in humans is typically a mild to moderate reduction in systolic, diastolic and mean arterial blood pressure associated with a reflex increase in heart rate. Rarely, significant hypotension and tachycardia have been observed.

Pharmacokinetics

Intravenously administered adenosine is rapidly cleared from the circulation via cellular uptake, primarily by erythrocytes and vascular endothelial cells. This process involves a specific transmembrane nucleoside carrier system that is reversible, nonconcentrative, and bidirectionally symmetrical. Intracellular adenosine is rapidly metabolized either via phosphorylation to adenosine monophosphate by adenosine kinase, or via deamination to inosine by adenosine deaminase in the cytosol. Since adenosine kinase has a lower K_m and V_{max} than adenosine deaminase, deamination plays a significant role only when cytosolic adenosine saturates the phosphorylation pathway. Inosine formed by deamination of adenosine can leave the cell intact or can be degraded to hypoxanthine, xanthine, and ultimately uric acid. Adenosine monophosphate formed by phosphorylation of adenosine is incorporated into the high-energy phosphate pool. While extracellular adenosine is primarily cleared by cellular uptake with a half-life of less than 10 seconds in whole blood, excessive amounts may be deaminated by an ecto-form of adenosine deaminase. As Adenoscan requires no hepatic or renal function for its activation or inactivation, hepatic and renal failure would not be expected to alter its effectiveness or tolerability.

Clinical Trials

In two crossover comparative studies involving 319 subjects who could exercise (including 106 healthy volunteers and 213 patients with known or suspected coronary disease), Adenoscan and exercise thallium images were compared by blinded observers. The images were concordant for the presence of perfusion defects in 85.5% of cases by global analysis (patient by patient) and up to 93% of cases based on vascular territories. In these two studies, 193 patients also

had recent coronary arteriography for comparison (h althy volunteers were not catheterized). The sensitivity (true positive Adenoscan divided by the number of patients with positive (abnormal) angiography) for detecting angiographically significant disease (≥50% reduction in the luminal diameter of at least one vessel) was 64% for Adenoscan and 64% for exercise testing, while the specificity (true negative divided by the number of patients with negative angiograms) was 54% for Adenoscan and 65% for exercise testing. The 95% confidence limits for Adenoscan sensitivity were 56% to 78% and for specificity were 37% to 71%.

Intracoronary Doppler flow catheter studies have demonstrated that a dose of intravenous Adenoscan of 140 mcg/kg/min produces maximum coronary hyperemia (relative to intracoronary papaverine) in approximately 95% of cases within two to three minutes of the onset of infusion. Coronary blood flow velocity returns to basal levels within one to two minutes of discontinuing the Adenoscan infusion.

INDICATIONS AND USAGE

Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately (See **WARNINGS**).

CONTRAINDICATIONS

Intravenous Adenoscan (adenosine injection) should not be administered to individuals with.

1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS

Fatal Cardiac Arrest, Life Threatening Ventricular Arrhythmias, and Myocardial Infarction

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

Sinoatrial and Atrioventricular Nodal Block

Adenoscan (adenosine injection) exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block

with Adenoscan, including first-degree (2.9%), second-degree (2.6%), and third-degree (0.8%) heart block. All episodes of AV block have been asymptomatic, transient, and did not require intervention. Adenoscan can cause sinus bradycardia. Adenoscan should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenoscan should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hypotension

Adenoscan (adenosine injection) is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflex mechanism are able to maintain blood pressure and tissue perfusion in response to Adenoscan by increasing heart rate and cardiac output. However, Adenoscan should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenoscan should be discontinued in any patient who develops persistent or symptomatic hypotension

Hypertension

Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenoscan (adenosine injection) is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO_2 causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenoscan has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenoscan should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g , emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction and bronchospasm (e.g , asthma)

Adenoscan should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS

Drug Interactions

Intravenous Adenoscan (adenosine injection) has been given with other cardioactive drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without apparent adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, Adenoscan should be used with caution in the presence of these agents.

The vasoactive effects of Adenoscan are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenoscan in the presence of these agents has not been systematically evaluated.

The vasoactive effects of Adenoscan are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the presence of dipyridamole has not been systematically evaluated.

Whenever possible, drugs that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of Adenoscan.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential of Adenoscan (adenosine injection). Adenosine was negative for genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations.

Fertility studies in animals have not been conducted with adenosine.

Pregnancy Category C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether Adenoscan can cause fetal harm when administered to pregnant women, Adenoscan should be used during pregnancy only if clearly needed.

Pediatric Use

The safety and effectiveness of Adenoscan in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

ADVERSE REACTIONS

The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Flushing	44%
Chest discomfort	40%
Dyspnea or urge to breathe deeply	28%
Headache	18%
Throat, neck or jaw discomfort	15%
Gastrointestinal discomfort	13%
Lightheadedness/dizziness	12%
Upper extremity discomfort	4%
ST segment depression	3%
First-degree AV block	3%
Second-degree AV block	3%
Paresthesia	2%
Hypotension	2%
Nervousness	2%
Arrhythmias	1%

Adverse experiences of any severity reported in less than 1% of patients include:

Body as a Whole

Back discomfort; lower extremity discomfort; weakness

Cardiovascular System

Nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause,

sweating; T-wave changes; hyp rtension (systolic blood pressure > 200 mm Hg)

Central Nervous System
Drowsiness; emotional instability; tremors

Genital/Urinary System
Vaginal pressure; urgency

Respiratory System
Cough

Special Senses
Blurred vision, dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort

Post Marketing Experience (see **WARNINGS**)
The following adverse events have been reported from marketing experience with Adenoscan. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, (3) strength of causal connection to the drug, or a combination of these factors

Body as a Whole
Injection site reaction

Central Nervous System
Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness

Digestive
Nausea and vomiting

Respiratory
Respiratory arrest

OVERDOSAGE
The half-life of adenosine is less than 10 seconds and side effects of Adenoscan (when they occur) usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed. Methylxanthines, such as caffeine and theophylline, are competitive adenosine receptor antagonists and theophylline has been used to effectively terminate

persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg slow intravenous injection) was needed to abort Adenoscan side effects in less than 2% of patients.

DOSAGE AND ADMINISTRATION

For intravenous infusion only.

Adenoscan should be given as a continuous peripheral intravenous infusion. The recommended intravenous dose for adults is 140 mcg/kg/min infused for six minutes (total dose of 0.84 mg/kg).

The required dose of thallium-201 should be injected at the midpoint of the Adenoscan infusion (i.e., after the first three minutes of Adenoscan). Thallium-201 is physically compatible with Adenoscan and may be injected directly into the Adenoscan infusion set

The injection should be as close to the venous access as possible to prevent and inadvertent increase in the dose of Adenoscan (the contents of the IV tubing) being administered.

There are no data on the safety or efficacy of alternative Adenoscan infusion protocols.

The safety and efficacy of Adenoscan administered by the intracoronary route have not been established.

The following Adenoscan infusion nomogram may be used to determine the appropriate infusion rate corrected for total body weight:

Patient Weight		Infusion Rate
kg	*lbs*	*mL/min*
45	99	2.1
50	110	2.3
55	121	2.6
60	132	2.8
65	143	3.0
70	154	3.3
75	165	3.5
80	176	3.8
85	187	4.0
90	198	4.2

This nomogram was derived from the following general formula:

$$\frac{0.140\ (\text{mg/kg/min}) \times \text{total body weight (kg)}}{\text{Adenoscan concentration (3 mg/mL)}} = \text{Infusion rate (mL/min)}$$

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Adenoscan (adenosine injection) is supplied as 20 mL and 30 mL vials of sterile, nonpyrogenic solution in normal saline.

NDC 0469-0871-20 Product Code 87120
60 mg/20 mL (3 mg/mL) in a 20 mL single-dose, flip-top glass vial, packaged individually and in packages of ten.

NDC 0469-0871-30 Product Code 87130
90 mg/30 mL (3 mg/mL) in a 30 mL single-dose, flip-top glass vial, packaged individually and in packages of ten.

Store at controlled room temperature 15°-30°C (59°-86°F)

Do not refrigerate as crystallization may occur. If crystallization has occurred, dissolve crystals by warming to room temperature. The solution must be clear at the time of use.

Contains no preservative. Discard unused portion.

Rx only

Marketed by:
Astellas Pharma US, Inc.
Deerfield, IL 60015-2548

Manufactured by:
Hospira, Inc.
Lake Forest, IL 60045 USA

Revised: July 2005

McDonnell Boehnen Hulbert & Berghoff
Law Offices

Fax transmittal

To	Examiner Crane	Date	September 14, 2006
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Fax	571-273-0651	Direct	312 913 2123
Phone		Email	hughes@mbhb.com
Copy To		C/M	
Pages, with cover	11		

Re: U.S. Patent Application Serial No. 10/629,368
MBHB Case No. 02-479-C

Dear Examiner Crane:

Attached hereto is a copy of Appendix C which accompanied Applicant's Reply to the May 31, 2006 Office Action for the above-identified patent application.

Very truly yours,

A. Blair Hughes
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